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Conization and healthcare use: a population-based register study

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The aim of this study was to assess whether negative psychological consequences of conization reported in questionnaire studies translated into increased use of the healthcare services that could relieve such symptoms. This was a population-based register study comparing women undergoing conization with a control group of women with normal cytology results. Data were derived from Danish registers. Using the difference-in-differences method, we measured contacts with general practitioners (GPs), hospitals, psychiatrist/psychologists, and use of anxiolytic and antidepressant prescription drugs over 5 years 'before' and 'after' the conization in the study group, and in comparable periods in the control group. During the 'before' period, women who later had a conization had greater contact with GPs and hospitals, and slightly more contact with psychiatrist/psychologists, than control women. In both groups, healthcare use increased significantly from the 'before' to the 'after' period. For contacts with GPs and hospitals, the increase was significantly larger for the conization group than for the control group, but this could be attributed to the standard postconization follow-up process. In the 'before' period, women who later had a

conization used fewer drugs than women of the control-group, but their drug use increased similarly over time. The conization event did not result in an increased use of the healthcare services that could relieve potential negative side effects. However, women who underwent a conization seemed to constitute a select group as they already used GPs and hospitals more frequently, and anxiolytic and antidepressant drugs less frequently, than other women in the years 'before' the conization event. *European Journal of Cancer Prevention* 00:000–000 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Treatment of screen-detected cervical intraepithelial neoplasia (CIN) has reduced the incidence of, and mortality from, cervical cancer (International Agency for Research on Cancer (IARC), 2005). CIN lesions can be both progressive and nonprogressive, but there is currently no method available to identify progression potential. Therefore, treatment is normally recommended for all cases of high-grade CIN (Andersen *et al.*, 2001). Currently, the most common treatment is large loop excision of the transformation zone (LLETZ), which is also known as a loop electrosurgical excision procedure. This is a minor surgical procedure, typically performed in an outpatient setting, and is highly effective in preventing progression to cervical cancer.

In Denmark, with its high background risk of cervical cancer, but an effective nationwide screening program, 14–16% of women have undergone CIN treatment during their lifetime (Barken *et al.*, 2012). This has led to a decrease in the incidence of cervical cancer, but has also resulted in an increased number of overtreatment cases (Barken *et al.*, 2012). Similar patterns have been observed in other countries (Raffle *et al.*, 2003).

LLETZ may cause minor, immediate side effects, such as pain, discharge, and bleeding (Sharp *et al.*, 2009). Whether treatment may potentially lead to adverse obstetric outcomes has been debated (Arbyn *et al.*, 2008; Bevis and Biggio, 2011). In Denmark, LLETZ has been found to be associated with preterm delivery (Noehr *et al.*, 2009). Several studies have reported negative psychological consequences when comparing women undergoing LLETZ with other women (Frederiksen *et al.*, 2015). However, these studies all used psychometric measurement, which might be prone to recall and reporting biases. Furthermore, these studies only compared the two groups of women following treatment, which leaves them susceptible to considerations of selection bias.

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Against this background, we carried out a population-based, register study of the potential impact of LLETZ treatment on women's use of healthcare services. Our study included all women undergoing LLETZ in Denmark between 2002 and 2005, and a control group of screened women. All data on healthcare use were collected independently from the LLETZ treatment data. To control for a potential selection bias, we included data from the time periods 'before' and 'after' LLETZ treatment.

Materials and methods

Cervical cancer screening and conization in Denmark

In the 1960s, organized, population-based cervical screening started in parts of Denmark, and opportunistic screening became widespread after 1969 (Lyng *et al.*, 2006). The first national guideline recommending the screening of women aged between 23 and 59 years of age, every third year, was issued in 1986. In 2007, a new guideline recommended screening every third year for women aged 23–50 years, and every fifth year for women aged 50–65 years. Human papillomavirus (HPV) testing also became a recommendation for women older than the age of 30 years, as triage for atypical squamous cell of undetermined significance, for control after conization, and as a check-up test for women aged 60–64 years (Sundhedsstyrelsen, 2012). Screening coverage in Denmark is around 75% (DKLS, 2012).

In 2001, the first national guideline for CIN treatment was established, and this guideline remained unchanged throughout our study period. Treatment was recommended if a cervical biopsy showed CIN2, CIN3 or persisting CIN1 for more than 12 months (Andersen *et al.*, 2001). The recommended treatment was colposcopy-guided LLETZ excision of the transformation zone.

CIN treatment was performed either in hospitals (both in-patient and outpatient) or in private gynecological clinics. CIN treatment performed in hospitals was recorded from operation codes in the National Patient Register (Andersen *et al.*, 2011). CIN treatment performed by private gynecologists was recorded by payment codes in the National Health Service Register (Prendiville, 1995). Specimens from CIN treatment were recorded using topography codes in the Danish Pathology Data Bank (Patobank), which, during our study period, included almost all specimens from both public and private sectors, except from Copenhagen municipality, which was therefore excluded from our analysis (Pedersen, 2011). The operation, payment, and topography codes used in the three registers did not enable distinction between LLETZ and cold-knife or laser conization, but from the late 1990s, LLETZ became the preferred modality for CIN treatment (Bjerregaard and Larsen, 2011). For convenience, we use the term 'conization' in this paper. From a previous study, we know that destructive treatment and hysterectomy constituted 16% of CIN treatment in the relevant time period (Barken *et al.*, 2012), and these CIN patients were not included in this study.

Design

Our 'exposed' group included women registered in Denmark, aged between 23 and 59 years, and having undergone their first conization during the period 2002–2005. For each of these women, we studied healthcare use during a 10-year period: from 5 years before ('before' period) to 5 years after ('after' period) conization. The women had to have lived in Denmark throughout this 10-year period.

The 'non-exposed' group of this study comprised all women aged 23–59 years with a normal cytology result between 2002 and 2005 and neither CIN nor cervical cancer in the 'before' period. For each of these women, we studied healthcare use during the 5 years before ('before' period) and the 5 years after ('after' period) their normal cytology result.

Contact with general practitioners (GPs) and psychiatrists/psychologists (PSYs) was measured by the number of contacts with patients. A contact could include a consultation, telephone or e-mail consultation, referral to a specialist or a hospital, renewal of a prescription, or a home visit. Hospital use was measured by the number of hospital contacts, including both in-patient and outpatient procedures. Finally, we measured the use of painkillers or anxiolytic and antidepressant prescription drugs by the number of 'defined daily dosages (DDDs)' for drugs defined by selected 'Anatomical Therapeutic Chemical classification' (ATC) codes. DDD is the assumed daily maintenance dose administered for the main indication as monotherapy. We included opioids ATC N02A, antiepileptic ATC N03, psycholeptic ATC N05, psychoanaleptic ATC N06, and other nervous system drugs ATC N07.

Other variables were age and region. Age was divided into 23–32, 33–43, and 43–59 year categories. Denmark was divided into three regions: 'Capital' (Copenhagen and Frederiksberg municipalities), 'Islands' (old Frederiksborg, Roskilde, Vestsjælland, Storstrøm, Bornholm, and Fyn counties), and 'Jutland' (old Sønderjylland, Ribe, Vejle, Ringkøbing, Århus, Viborg, and Nordjylland counties).

Data sources

Data on conization were retrieved from the three registers described above. Data on normal cytology results were obtained from the Patobank. Data on date of birth and residence in Denmark, during the 10-year study period, were obtained from the Danish Civil Registration System (Kildemoes *et al.*, 2011). Data on contact with GPs and psychologist/psychiatrist were retrieved from the National Health Service Register. Data on hospital contact were retrieved from the National Patient Register. Data on the use of prescribed and purchased drugs were obtained from the Danish National Prescription Registry (Christensen *et al.*, 2011). The data from these sources were linked through each woman's unique personal identification number, which is assigned to all individuals with a permanent address

in Denmark and used for identification in all registers. Data were approved by the Danish Data Protection Agency.

Statistical analysis

We used the difference-in-differences method, where the data provided four points of interest for each type of healthcare use: number of contacts in the 'before' period for exposed women, number of contacts in the 'before' period for nonexposed women, number of contacts in the 'after' period for exposed women, and number of contacts in the 'after' period for nonexposed women. The aim of the analysis was to assess the effect of exposure on the changes in the number of healthcare interactions from the 'before' to the 'after' period.

General linear mixed models and least square means were applied to the data, and the statistical significance of the mean number of contacts for exposed and non-exposed women, in the 'before' and 'after' periods, their confidence intervals, and their statistical significance was calculated. We also calculated the differences between the 'before' and the 'after' period for exposed women and for nonexposed women, their confidence intervals, and statistical significance.

Secondary analyses, stratified by age and region, were carried out using the same statistical model. These analyses were repeated using generalized linear mixed models with different distributions and link functions (e.g. Gaussian, Poisson, negative binomial), leading to almost equivalent results. This analysis was carried out using R, version 3.2.0 (The R foundation for Statistical Computing, Vienna, Austria).

Results

In total, 14 957 women who underwent a conization and 923 094 who did not undergo a conization were included in the study (Table 1). Approximately half, 52%, of the women in the conization group were aged between 23 and 32 years, and 43% of the women who did not undergo conization were in the age group 43–59 years. These women were distributed evenly across regions.

Around 40% of the women in both groups had 24–53 contacts with their GPs in both the 'before' and the 'after' periods (Table 1). The majority of women had no hospital contact (56–69%), nor any contact with a PSYs (88–93%). Just under half of the women had used at least one of the drugs studied, and around 15% had used 260 or more DDDs.

Contact with general practitioners

Women with conization had a mean number of 62.2 contacts with their GP in the 'before' period and 69.5 in the 'after' period, which represents a change of 7.29 [95% confidence interval (CI): 6.63–7.94] (Fig. 1). Women without conization had 54.7 GP contacts in the 'before' period and 61.1 in the 'after' period, representing a change of 6.36 (95% CI: 6.28–6.45). Women with conization showed a greater increase

Table 1 Distribution of study population by age and region at the time of the event and by use of healthcare services

	Women with conisation (N = 14 957) [n (%)]	Women without conisation (N = 923 094) [n (%)]		
Age at event (years)				
23–32	7757 (52)	250 105 (27)		
33–42	4741 (32)	271 878 (30)		
43–59	2459 (16)	401 111 (43)		
Region at event				
Capital ^a	4314 (29)	199 794 (22)		
Islands ^b	3704 (25)	252 241 (27)		
Jutland	6939 (46)	471 059 (51)		
	Before (%)	After (%)	Before (%)	After (%)
Contacts to GP				
0–23	2171 (15)	1594 (11)	217 264 (23)	185 663 (20)
24–53	6008 (40)	5395 (36)	362 109 (39)	336 976 (37)
54–79	3324 (22)	3533 (24)	170 489 (18)	182 844 (19)
80+	3454 (23)	4435 (29)	173 232 (20)	217 611 (24)
Contact to hospital				
0	8642 (58)	8416 (56)	635 419 (69)	630 077 (69)
1	3614 (24)	3252 (22)	165 066 (18)	157 657 (17)
2	1341 (9)	1574 (11)	63 173 (7)	67 377 (7)
3+	1360 (9)	1715 (11)	59 436 (6)	67 983 (7)
Contact with psychologist/psychiatrist				
0	13 587 (91)	13 102 (88)	856 469 (93)	834 757 (90)
1–4	510 (3)	573 (4)	21 237 (2)	25 246 (3)
5–9	365 (2)	478 (3)	17 547 (2)	22 739 (2)
10+	495 (3)	804 (5)	27 841 (3)	40 352 (5)
DDD of prescription drugs				
0	9229 (62)	8009 (54)	552 057 (60)	484 220 (52)
1–59	3196 (21)	3069 (21)	177 942 (19)	171 090 (19)
60–259	1037 (7)	1325 (9)	71 105 (8)	81 941 (9)
260+	1505 (10)	2554 (16)	121 990 (13)	185 843 (20)

DDD, defined daily dosages; GP, general practitioner.

^aCopenhagen and Frederiksberg municipalities.

^bOld Copenhagen, Frederiksborg, Roskilde, Vestsjælland, Storstrøm, Bornholm, and Fyn counties.

in their number of GP contacts over time, 0.93 more than women without conization ($P=0.006$).

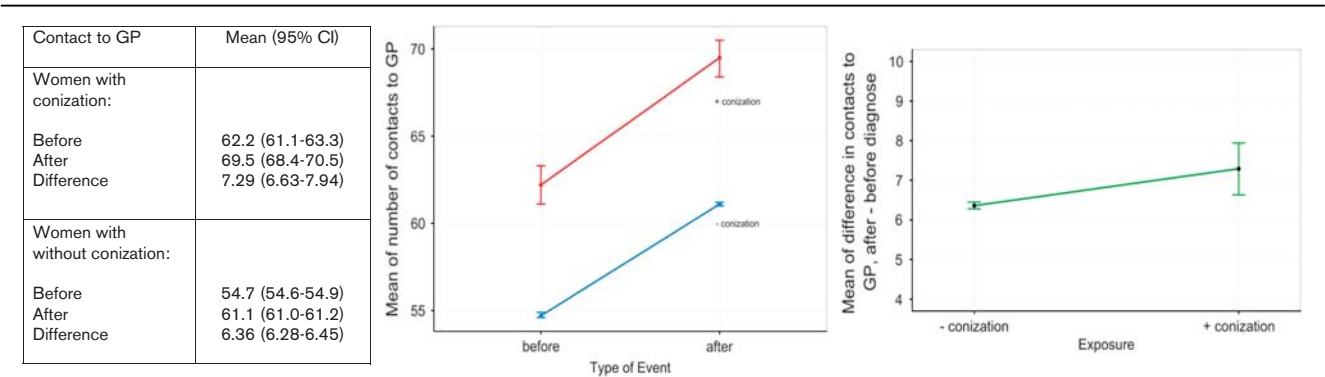
This pattern was observed in both the youngest (23–32 years) and the eldest (43–59 years) age groups, and in all regions. In the age group 33–42 years, the number of contacts with GPs was stable for women with conization, and slightly reduced for women without conization (Supplementary File 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A181>).

Contact with hospitals

Women with conization had a mean number of 0.860 hospital contacts in the 'before' period and 1.00 in the 'after' period, which represented a change of 0.141 (95% CI: 0.120–0.163) (Fig. 2). For women without conization, it was 0.613 'before' and 0.688 'after', representing a change of 0.075 (95% CI: 0.072–0.077). Women with conization increased their number of hospital contacts 0.066 more than women without conization ($P<0.001$).

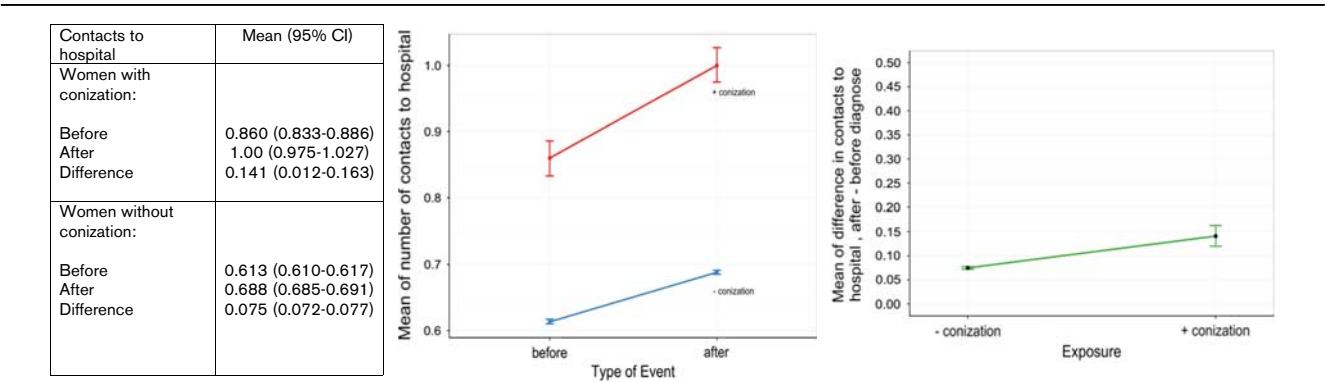
In the youngest age group, 23–32 years, and in the eldest age group, 43–59 years, and across all regions, the same pattern emerged. In the 33–42 year age group, the number of contacts with hospitals was stable for women with

Fig. 1



Mean number of contacts to GP by period (before/after) and exposure (with/without) and mean of differences in number of contacts to GP from 'after' minus 'before' period by exposure.

Fig. 2



Mean number of contacts with hospitals by period (before/after) and exposure (with/without) and mean differences in the number of admissions to hospital from 'after' minus 'before' period by exposure. CI, confidence interval.

conization and slightly decreased for women without conization (Supplementary File 2, Supplemental digital content 1, <http://links.lww.com/EJCP/A181>).

Contact with psychologists/psychiatrists

In the 'before' period, women with conization had a mean number of contacts with PSYs of 0.913, which increased to 1.480 'after', representing a change of 0.563 (95% CI: 0.477–0.649) (Fig. 3). Women without conization started out with effectively the same mean number, 0.854, which increased to 1.28 in the 'after' period, representing a difference of 0.423 (95% CI: 0.412–0.434). The increase over time was thus slightly larger for women with conization than for those without ($P=0.01$). This pattern was found across all age and region groups (Supplementary File 3, Supplemental digital content 1, <http://links.lww.com/EJCP/A181>).

Use of prescription drugs

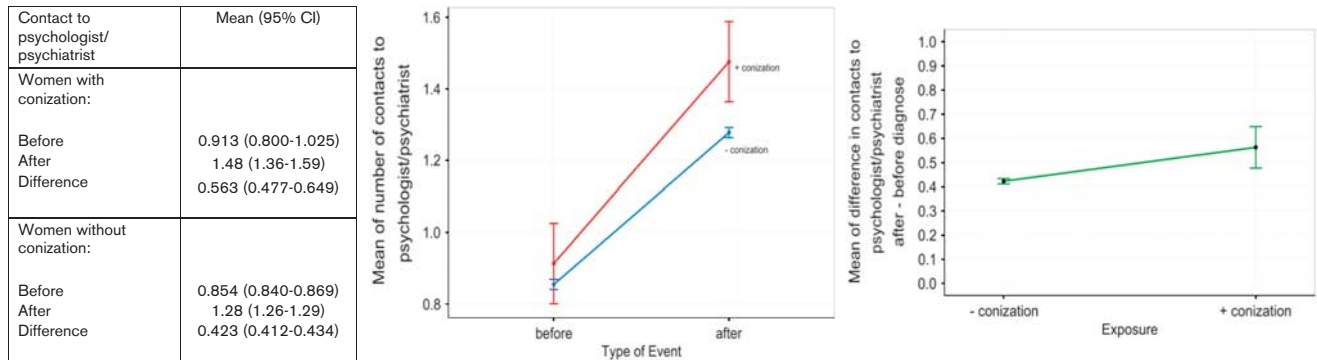
Women with conization used 156.8 DDDs in the 'before' period and 313.2 DDDs 'after', yielding a difference of

156.5 (95% CI: 147.9–165.1). Women without conization used 226.7 DDDs before and 383.0 DDD after, representing a difference of 156.3 (95% CI: 155.2–157.4) (Fig. 4). This increase over time was similar across the two groups ($P=0.958$). When stratifying for age and region, this pattern persisted for the youngest and eldest age groups, but not for the 23–32 year age group, where no significant difference was found between the two groups of women (Supplementary File 4, Supplemental digital content 1, <http://links.lww.com/EJCP/A181>).

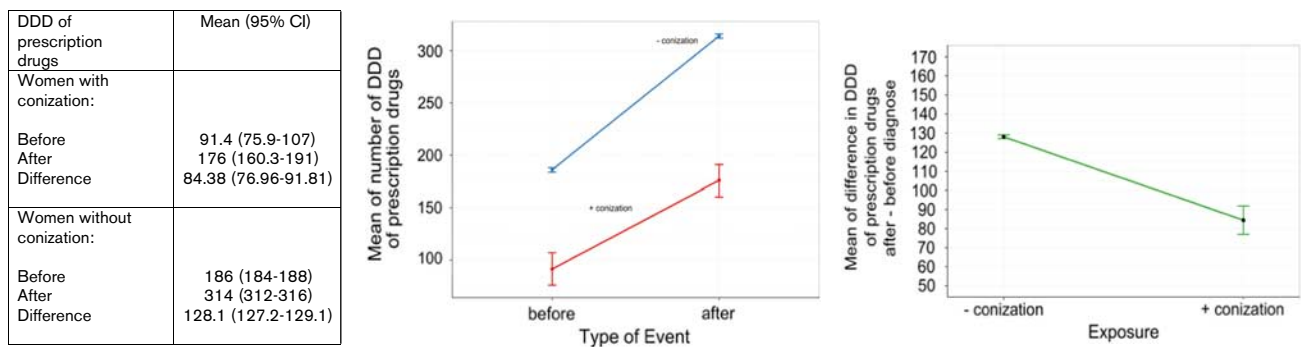
Discussion

Main findings

This study investigated the association between conization and healthcare use in a large, population-based register study. Three important findings should be highlighted here and will be discussed further below. First, there was a selection effect, which was observed to be inconsistent across the four studied types of healthcare services. In the 'before' period, women who later had a conization had more

Fig. 3

Mean number of contacts to psychologist/psychiatrist of by period (before/after) and exposure (with/without) and mean of differences in number of contacts to psychologist/psychiatrist from 'after' minus 'before' period by exposure.

Fig. 4

Mean number of defined daily dosages (DDD) of prescription drugs by period (before/after) and exposure (with/without) and mean differences in DDD of prescription drugs from 'after' minus 'before' period by exposure. CI, confidence interval.

contact with GPs and hospitals, and an almost similar amount of contact with PSYs than women who later did not undergo a conization procedure. However, surprisingly, for drug use, the opposite pattern was observed as women who later had a conization used significantly fewer anxiolytic and antidepressant drugs in the 'before' period than women who later did not undergo conization.

Second, an aging effect was present, where the use of healthcare services increased from the 'before' to the 'after' period for all women, except for their contact with GPs and hospitals for women aged 33–42 years who did not have a conization. Finally, an apparent exposure effect was present, where contact with GPs and hospitals increased to a significantly greater extent from the 'before' to the 'after' period of women who underwent conization in relation to women who did not. For contact with PSYs, this exposure effect was borderline significant, and for drug use it was absent. These observed effects will be discussed in the following sections.

Are women who undergo conization a select group?

We found that women who underwent conization later in life had already in the period 'before' their procedure had more GP contacts than women who did not. All women who undergo conization will, by definition, have had one extra contact with their GP in the period leading up to their procedure as they require a referral from the GP to the treating gynecologist. Women with abnormalities that start as an atypical squamous cell of undetermined significance/low-grade squamous intraepithelial lesion and that result in the need for a conization procedure may have had additional 1–2 GP contacts in the period 'before' conization, as part of the diagnostic process, with repeated cytology required before they are referred to a gynecologist. However, these conization-related GP contacts cannot explain the additional 5.5 GP contacts in the exposed than in the nonexposed group in the period 'before' conization. It therefore seems reasonable to conclude that the women who later underwent conization constituted a select group with above average GP contact. The explanation for this selection effect is currently

unknown. An in-depth study is required to identify the clinical background for this extra interaction with healthcare professionals.

Does conization increase the use of healthcare?

At least part of this greater increase in the number of GP contacts over time, for exposed women compared with non-exposed women, of 0.93, might be explained by postconization follow-ups sometimes being performed by GPs. The slightly, but statistically significant, greater increase in hospital contacts for exposed women, in comparison with nonexposed women, of 0.066 contacts, could also be because of post-conization follow-ups being performed in the hospitals that performed their procedures. It therefore seems reasonable to conclude that conization did not increase contact with GPs and hospitals beyond what could be explained reasonably by postconization controls.

Women without conization

In terms of the use of prescription anxiolytic and antidepressant drugs, women without conization showed a higher use in the 'before' period than women who underwent conization later (Fig. 4). This pattern was unexpected. It could be that women who used these drugs had less sexual activity and therefore had a lower risk of developing precancer lesions. A large, questionnaire-based study in Denmark showed an increased risk of sexual dysfunction in women with poor self-rated health, odds ratio: 1.91 (95% CI: 1.087–3.37), and mental health problems, odds ratio: 2.59 (95% CI: 1.60–4.22) (Christensen *et al.*, 2011).

Strengths and limitations

By focusing on the use of healthcare, we were able to characterize women undergoing conization and women having normal cytology results both 'before' and 'after' these events took place. This helped us to identify a possible selection effect, which previous studies have failed to show. We used population-based data from well-maintained Danish registers, thus excluding reporting and recall biases, and ensuring almost no loss of follow-up.

Limitations included the inability to separate LLETZ from other conization modalities, and the fact the around 16–23% of CIN treatments in 2002–2005 were performed by procedures other than conization (Barken *et al.*, 2012).

Interpretations

Psychological outcomes following CIN diagnosis or treatment have been studied extensively by psychometric measurement. Our previous review (Frederiksen *et al.*, 2015) showed that in these studies, a CIN diagnosis and/or CIN treatment had consistently been associated with a negative psychological impact.

No other study has investigated the impact of conization on women's healthcare usage. It is, however, reasonable to expect that psychological problems will lead to the use of healthcare. In Denmark, where access to the GP is free of

charge, about one-third of all contacts with GPs concern psychological disorders, and an even greater proportion of contacts is related to emotional problems (Davidsen, 2008). In terms of our data from the period 'after' conization, these were in line with results from studies based on psychometric measurement. We found that women in the conization group were more intensive users of healthcare services, apart from the use of anxiolytic and antidepressive drugs, than women who did not undergo conization. However, taking into account our data from the period 'before' conization, our study indicated that the difference between the two groups of women derived from a selection effect rather than from exposure to conization itself.

On the basis of our results, we recommend that a possible selection effect should be considered in the handling of women with psychological problems that follow a conization procedure. This selection effect could indicate that the psychological problems derive not from the conization itself, but from other problems encountered by this group of patients. Therefore, a woman's reaction to conization should ideally be seen in light of her general medical history.

In generations of women HPV-vaccinated before sexual debut, the frequency of high-grade CIN lesions is expected to reduce to one half of current levels (Hestbech *et al.*, 2015). Another way of reducing the number of conization procedures required may be to reduce the risk of HPV reinfection by male partners using condoms for a certain period of time (Hogewoning *et al.*, 2003; Munk *et al.*, 2012a, 2012b). Nevertheless, women undergoing conization will, for years to come, remain a large group for whom adequate care is needed. In the provision of this care, a woman's medical history before conization should also be taken into account.

Conclusion

This study was carried out to investigate whether the negative psychological consequences of conization reported by questionnaire studies, etc. translated into an increased use of the healthcare services that could be used to relieve such symptoms. Our study showed this not to be the case. However, women who underwent conization had significantly more contact with their GPs and hospitals than women who did not undergo conization, even 'before' the event. This indicates that, in treating women with psychological problems, following a conization procedure, their medical history over the period before conization should also be taken into account.

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M.E.F, M.V.P.B., E.L.: designed the study, analyzed the data, interpreted the results, and wrote this manuscript. P.T.J., C.R., J.H.: participated in the interpretation of

data, and in the writing of the final manuscript. All authors made the decision to submit.

Conflicts of interest

E.L. and C.R. work on a study that includes collaboration with four manufacturers of HPV assays: Qiagen, Roche, Hologic/Gen-Probe, and Genomica. E.L. and C.R. received neither salary nor bonuses from any of these companies. E.L. has been an advisor for Roche and Astra-Zenica, for which fees have been paid to her institution. For the remaining authors there are no conflicts of interest.

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